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On the Uric Acid Excretion
Of Normal Men

Six Year Medical Course

B. A.

1908

ON THE URIC ACID EXCRETION

OF NORMAL MEN

By

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THESIS

FOR THE

DEGREE OF BACHELOR OF ARTS IN

THE SIX YEAR MEDICAL COURSE

COLLEGE OF SCIENCE

University Of Illinois

1908.

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UNIVERSITY OF ILLINOIS

May 28 1908.

THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

PAUL J. HANZLIK.

ENTITLED ON THE URIC ACID EXCRETION OF NORMAL MEN.

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF BACHELOR OF ARTS.

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C O N T E N T S

I. INTRODUCTION.

Perhaps no purin body has been the cause of more profound speculation than uric acid. At first it was considered merely as a urinary constituent. In 1776 Scheele discovered uric acid in urinary calculi, Liebig and Wöhler studied it and showed its close relationship to urea. Liebig discovered that when uric acid and lead peroxide are heated together, urea, allantoin, and oxalic acid are formed. This was a mere fact of chemistry, but its relation to metabolism has formed only of late a subject for discussion.[1]

1. Macleod: Recent Advances in Physiology, 1907, p. 387.

Whatever may be the meaning of an increased or decreased uric acid elimination, nevertheless, it has been proven only recently how these variations may be brought about. The older chemists whose work has been disputed by recent investigators laid considerable stress on a host of substances, such as drinking water and alkalies, as to their influence on the elimination of uric acid.[2]

2. Schöndorff: Archiv für die gesammte Physiologie, XLVI, pp. 529-551.

Genth found that large quantities of water would decrease the excretion of uric acid.[3] Schöndorff has pointed out this observation to be wrong due to an inaccurate method of analysis. This observer proves further that copious ingestion of water has no

influence on the elimination of uric acid.[2]

3. Genth: cited by Schöndorff: Loc. cit.

Today it is asserted as proven by the classic experiments of Burian and Schur[4] as well as the more recent ones of Folin[5] that there are two kinds of uric acid excreted.

4. Burian and Schur: Archiv für die gesammte Physiologie, 1902, XC, p. 368; LXXXVII, 1901, p. 239. LXXX, 1900, p. 241.

5. Folin: American Journal of Physiology, XIII, No. I, p. 45.
Folin: Ibid., XIII, No. I, 1905. p. 66.

Both have their origin from nuclein material which is either supplied by food or from the nucleins of cells undergoing destruction in the organism. Folin, having arrived at somewhat different results, does not agree with Burian and Schur in their conclusions. This, however, does not alter the main fact that uric acid owes its origin to nucleins. The opinion seems to prevail that Folin has drawn his conclusions rather more accurately. The observations of Sivén,[6] Rockwood,[7] and others have led to the same conclusions as those of Burian and Schur.

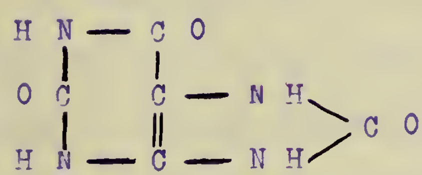
6. Sivén: Skandinavisches Archiv für Physiologie, 1901, XI, p. 308.
7. Rockwood: American Journal of Physiology, 1905, XII, p. 38.

Chittenden[8] accepts the view of Folin. Macleod and Haskins[9] observed similar results to those of Burian and Schur. The work of these investigators will be discussed later.

8. Chittenden: The Nutrition of Man, 1907, pp. 144-152.
9. Macleod and Haskins: Journal of Biological Chemistry, 1906, II, p. 231.

II. U R I C A C I D: Its structure, Origin and Excretion.

As has already been stated, uric acid is a purin body. Other substances containing the purin ring are xanthine, hypoxanthine, guanine, adenine, heteroxanthine, 1-methylxanthine and paraxanthine. Some of these substances are capable of affecting the excretion of uric acid in man, but not in the same degree as nuclein itself. The formula for uric acid as given by Fischer[10] is:



It is a diureid consisting of two molecules of urea linked together by a carbon residue.[11] Uric acid has been

10. Fischer: Berichte der deutsch. Chem. Gesell., XXXII, p. 435.
11. Macleod: Recent Advances in Physiology, 1907, p. 387.

synthesized by Horbaczewski[12] by fusing urea and glycocoll.

12. Horbaczewski: Chemie Lekařská, Dil III, Chemie fysiologická, část II, 1908, p. 535.

It has also been prepared from isodialuric acid and urea,[13] and is easily obtained by boiling isouric acid with hydrochloric acid.[14] Fischer and Ach have prepared uric acid from pseudouric acid by heating with oxalic acid to 145°C.[15] With strong oxidizing

13. Behrend and Roosen: Berichte der deutsch Chem. Gesell, Chap. XXI.
14. E. Fischer and Tüllner: ibid. XXXV.
15. E. Fischer and Ach: ibid. XXVIII.

agents such as nitric acid, uric acid is decomposed to urea and alloxan. Mild oxidizers such as potassium permanganate change it to allantoin, a compound similar to uric acid. Strong heat decomposes it into urea, hydrocyanic acid, cynauric acid and ammonia. When a large excess of uric acid is present in the tissues of cats and dogs, allantoin is found in their urine.

Uric acid in mammalia does not so far as is known arise from any synthetic process. In birds, however, it is synthesized within the organism. In both birds and mammalia the end-product of metabolism is urea, but in the former two molecules of urea are synthesized with a carbon residue and excreted as uric acid, while in the latter the urea is eliminated in the urine as such. For this reason it has been suggested also that the small quantities of uric acid in mammalia is a remnant of an evolutionary process which betrays the development of birds and mammalia from some common stock.[16] If in some way this synthesis could be prevented in birds, urea would be the final excreted product. Birds excrete a very small amount of urea which is perhaps due to incomplete synthesis of uric acid.

16. Macleod: Recent Advances in Physiology, 1907, p. 387.

Urea fed to birds appears as uric acid in the excrement. Uric acid given internally to mammalia appears in the urine as urea.

Uric acid was considered as a precursor of urea, and that it appeared only as an intermediary product from the digestion of protein in the organism and upon oxidation finally yielded urea. Protein then was thought to be the parent substance of both uric acid and urea. Numerous observations, however, have proven that this is not the case. It has been demonstrated by Horbaczewski[17] that uric acid is formed from those nucleo-proteins rich in hypoxanthine, xanthine, adenine and guanine.

17. Horbaczewski: Chemie Lekařská, Díl III, chem. fysiologická, část II, 1908, p. 536.

He digested the pulp of spleen in water with the exclusion of air and found that the products consisted of purin bases. When air was passed through the mixture uric acid was obtained. Since the pulp of spleen is rich in nucleins, particulary the nucleo-proteins behaving like purins or nucleins, there was no doubt that purin bodies or uric acid could be obtained from them. Horbaczewski and his co-workers Sadoměra, Mrázek, and E. Formánek[18] showed further that purins or equivalent yields of uric acid can be obtained from the extracts of all animal organs where originally it was lacking or existed only as a modification. In a similar manner uric acid was obtained from nuclein.

18. Sadoměra, Mrázek, and Formánek: Časopis českých lekařů, 1891, p. 773.

Still further experiments showed that when nuclein was fed to lower animals and man there was an increase in the excretion of uric acid. From this Horbaczewski concluded that uric acid in

the body also comes from a breaking-down of nuclein. According to this uric acid and the nuclein principles, chiefly the purin bases, are formed from the changes that nucleo-proteins undergo in the mammalian organism, and that they obey laws different from those concerning the metabolism of other protein foods and substances containing nitrogen. These observations have been confirmed by many investigators and it must be admitted that uric acid can be produced from purine bases, either within or without the animal body, also that food rich in nucleins increases the excretion of uric acid and the purine bases.

The monumental work of Burian and Schur demonstrated the twofold origin of uric acid in the normal body. These two sources of uric acid are called the exogenous and the endogenous. The former name is applied to that portion of the uric acid excretion due to the purins of food. That uric acid which results from the breaking-down of nuclein material of the tissues of the organism is termed the endogenous. There is no doubt that when food purins are ingested they increase the excretion of urinary purins. The methyl-purins, caffeine and theobromine do not increase the excretion of uric acid when given in food, but do increase the purin-bases.[19]

19. Macleod: Recent Advances in Physiology, 1907, p. 387.

Determinations made by Burian and Hall[20] show that glands contain the greatest amount of purins, meat very much less so, while milk, eggs, and vegetables exceedingly small quantities.

20. Burian and Hall: Zeitschrift für physiologische Chemie, 1903, XXXVIII, p. 392.

Naturally enough for practical purposes a diet of milk, eggs, and vegetables could be constructed as purin-free and the effect of such a diet noticed. This has been done in many instances and the results obtained are similar, but often the deductions differ. Burian and Schur[21] conclude that the food purins are not excreted quantitatively in the urine.

21. Burian and Schur: Archiv für die gesammte Physiologie, 1900, LXXX, p. 241.

These investigators claim that the purin double-ring undergoes a decomposition to a lesser or greater degree, and only the residue goes over into the urine as urinary purin. The quantity of this residue differs for different food purins, for one and the same food-purin, but independent of the individuality. If now the total purins determined from the food taken are deducted from the total purins excreted we have left a value for the endogenous purin.

As to the origin of endogenous uric acid, there still remains a doubt. Burian and Schur,[22] although they decline to speak positively of a uric acid synthesis in a diet of carbohydrates, fat and protein, believe that there is a so-called "regeneration of endogenous urinary-purin" from purin-free material. Under similar dietary regimes they claim that

22. Burian and Schur: Archiv für die gesammte Physiologie, 1903, XCIV, p. 273.

different individuals exhibit different endogenous urinary-purin values. They do not state that both the exogenous and

the endogenous uric acid are intermediary nitrogenous products which undergo still further decomposition in the body. This was observed on a dog whose blood showed endogenous uric acid after extirpation of the kidney and the liver, but which did not show endogenous uric acid formation after extirpation of the kidney alone. This shows that the liver which concerns itself with the transformation of purins to uric acid is also a uric acid destroying organ. Other organs have been shown to possess similar properties. In fact Burian and Schur[23]

23. Burian and Schur: Archiv für die gesammte Physiologie, 1901, LXXXVII, p. 239.

suggest an "integral factor" with which the quantity of uric acid excreted during twenty-four hours must be multiplied in order to get the quantity of uric acid formed during this time. This "integral factor" is constant but different for different individuals. It would tend to show then that only that uric acid which escapes decomposition is excreted in the urine. This would include both the endogenous and exogenous uric acid. This would again be dependent on the relative degree of the circulation of the blood which carries the uric acid through the various organs including the liver and the kidney.

If a purin-free diet can sustain life, then the quantity of urinary purins cannot represent any value for hunger, for the mother substances of endogenous urinary purins are always built up again from purin-free food-stuffs.[24] During the purin

24. Burian and Schur: Archiv für die gesammte Physiologie, XCIV, 1903, p. 273.

free diet man excretes a quantity of endogenous urinary purins which is essentially determined through the individuality and the manner of living. On the contrary it is independent of the food within very broad boundaries.[25] In a purin diet the

25. Burian and Schur: Archiv für die gesammte Physiologie, 1905, XCIV, p. 273.

quantity of endogenous urinary purins remains unchanged under normal conditions. Burian and Schur also draw the conclusion that the mother-substances of endogenous urinary purins have a tendency to regenerate from purin-free material in the presence of food-purins. Objection has been raised to the diet of Burian and Schur. Folin,[26] who opposes it, selects a "starch-cream" diet consisting of arrowroot-starch 400 gms; cream 300 c.c. (15-20% fat) and 6 gms., of sodium chloride to season. This he claims to be entirely purin-free. The Burian and Schur diet contains potatoes which affect the excretion of uric acid according to Folin. As a result Folin arrives at

26. Folin: American Journal of Physiology, 1905, XIII, No. I, p. 66.

some interesting conclusions. "When the total amount of protein metabolism is greatly reduced, the absolute quantity of uric acid is diminished, but not nearly in proportion to the diminution in the total Nitrogen, and the percentage of the uric acid

nitrogen in terms of the total nitrogen is therefore much increased." Folin's tables show that the absolute quantity of uric acid eliminated on a "starch-cream" diet is not as great as on a protein diet.[27]

27. Folin: American Journal of Physiology, XIII, No. I, p. 66.

This investigator says further that the more the total protein metabolism is reduced, the more prominent in percent of the total urinary nitrogen becomes the uric acid nitrogen, and the most probable explanation of such a relative increase in the uric acid-nitrogen is, in his opinion, that at least a certain part of the uric acid represents the breaking down of living protoplasm which must be essential to the continuation of life. Folin differs with Burian and Schur also in that he finds no such sharp dividing line between endogenous uric acid from the uric acid produced under the influence of food. After a series of nine experiments be concludes that when total nitrogen elimination is very much diminished that the uric acid elimination is reduced. This reduction, however, is irregular and different for different persons, while the metabolic processes that determine the uric acid excretion may therefore be said to be in a relatively unstable equilibrium. The real difference then between Folin's and Burian and Schur's experiments is in the diet which would tend towards a difference in results. The general results of these observers are very similar, although their interpretations differ widely. Both

have followers.

The experiments of Sivén tend to show practically what Burian and Schur found. Rockwood[28] with a purin-free diet (similar

28. Rockwood: American Journal of Physiology, 1905, XII. p. 38.

to that of Burian and Schur) finds that the individual factor plays a very important part in the endogenous excretion, that it is very variable but constant in quantity for the same person. This result seems to coincide with that of Burian and Schur. He also observes further that excessive exercise may temporarily increase it, but that continual hard work will gradually diminish it to the normal endogenous plain. Hard exhaustive labor was found to be followed by a rise in the excretion of uric acid. This would seem to follow Folin's conclusion, that is, that sudden hard labor before the tissues become attenuated, or exhaustive labor tends to produce a breaking-down of the protoplasm of the cells. It would seem then that the nuclei of these destroyed cells would give origin to a greater output of endogenous uric acid. This may or may not be beneficial to the organism, depending on the locality, organ, or kind of tissue subject to this destruction.

Numerous observations show the interesting fact that uric acid in the animal organism undergoes almost complete destruction. Burian and Schur observed that both exogenous and endogenous uric acid in man undergo decomposition to about fifty per cent. According to this only half of the uric acid

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[illegible]

[illegible]

produced is excreted. How this decomposition is brought about has not yet been definitely ascertained. Schittenhelm[29] has

29. Schittenhelm: Zeitschrift für physiologische Chemie, XL, p. 121.

shown the existence of an oxidizing enzyme, a so-called uricolytic enzyme, in the kidneys. liver and muscles. In man the final product is urea, while in dogs on a rich purin diet consisting of thymus and pancreas a marked increase in allantoin was observed.[30] Minkowski[31] also observed a similar result. Wiener[32] maintains that glycocoll occurs as an intermediary product, especially in rabbits. This power

30. Salkowski: Zentralblatt für medizinische Wissenschaft, XXXVI, p. 929.
31. Minkowski: Zentralblatt inn. Med., XIX, No. 19.
32. Wiener: Archiv für exp. Pathologie und Pharmakologie, XL, p. 313 and XLII, p. 375.

of destroying uric acid by various organs differs with different animals. The so-called "integral-factor" of Burian and Schur by which the quantity of uric acid excreted in twenty-four hours must be multiplied would find here an application.

The mammalian organism possesses a limited ability to form uric acid by synthesis from urea and certain nitrogen-free substances.[33]

33. Burian and Schur: Archiv für die gesammte Physiologie, 1903, XCIV, p. 273.

No positive proof can be given whether such a synthesis exists in man. It can, however, be openly asserted that excess of protein, fat and carbohydrates possess no clear demonstrable

influence upon the uric acid excretion of men; that uric acid originating from the nucleins is partly endogenous and partly exogenous; that individuality plays an important factor in endogenous uric acid excretion and that there is a possibility of a uric acid destruction in man.

Besides variations in diet and individual differences, certain drugs and chemical compounds affect the excretion of uric acid under normal conditions. Drinking excessive quantities of water shows no effect on the excretion of uric acid, which however during an insufficiency is not evident.[34]

34. Mareš: Sbornik Lekařský, I, p. 263.

As was stated before Schöndorff as well as Schreiber ovserved no action of water on uric acid elimination. When fat or

35. Schöndorff: Archiv für die gesammte Physiologie, XLV, p. 529 and LXXI, p. 48.
36. Schreiber: Die Harnsäure etc Stuttgart 1899.

carbohydrates (butter or sugar) is added to a regular diet, a decrease in the elimination of uric acid occurs, while glycerol, on the other hand, notably increases the excretion of uric acid.[37]

37. Horbaczewski and Kaněra: Chemické Listky, XI, p. 1.

Sodium citrate and sodium bicarbonate given during a purin-free diet cause an increased excretion of endogenous purins according to Macleod and Haskins.[38]

38. Macleod and Haskins: Journal of Biological Chemistry, 1906, II, p. 231.

The use of alcohol is considered to have little or no effect on the excretion of uric acid, if any, it may cause a slight increase.[39]

39. Rosenfeld, Rosemann cited by Horbaczewski: Chemie Lekařská, Díl III, Chem. fysiologická, Část II, 1908, p. 540.

The recent observations of Beebe[40] indicate that the effect of alcohol is of a toxic nature on the liver, thereby interfering with the oxidation of uric acid by that organ. Beebe observes

40. Beebe: American Journal of Physiology, 1904, XII, p. 13.

that alcohol taken without food causes no increase, but administered with a diet of less purin content gives an increase in the excretion of uric acid. A maximum increase occurs at the same time after a meal as it does when purin food but no alcohol is taken. This observer believes that alcohol is rapidly absorbed and passes at once to the liver thereby interfering with the activities of a most important organ because of its toxic affect. Jackson and Blackfan[41] verified the findings of Beebe in that they observed an increase of from 25 to 50 per cent in the elimination of uric acid under like conditions of

41. Jackson and Blackfan: Albany Medical Annals, 1907, XVIII, p. 24.

alcohol administration. These authors also found an increase in the output of uric acid after the administration of certain drugs as colchicum and sodium salicylate. They offer the explanation that the rise in elimination is due to an increased

formation as a result of the decompostion of the nuclein-containing compounds of the cells. They conclude that the temporary beneficial effects of salicylates and colchicum observed clinically are the results of some secondary action possessed by these substances inasmuch as an increase of uric acid in the organism would increase the uric acid content of the blood and thus cause a tendency to deposit urates, as in gout for example. Pilocarpine increases, while quinine and atropine decrease the elimination of uric acid.[42] Formánek[43] who

42. Bohland cited from Maly's Jahresberichte, XXVI; Schreiber and Zandy ibid, XXX, cited by Hammarsten, Text-book of Physiological Chemistry trans., by Mandel, 1908, p. 569.

has studied the influence of hot and cold water baths finds it insignificant. Hot baths as well as cold baths produced an increase in the elimination of uric acid, differing with the individuality and intensities of over-heating and cooling. The explanation offered for the action of hot baths is that they cause an increase in body temperature and therefore may produce an over-heating of the organism with a consequent breaking-down of tissue protein. According to foregoing generalizations uric acid can only be produced from the breaking-down of nucleo-protein and not protein.

43. Formánek: Časopis českých lékařů, XXI, p. 781.

Observations on the elimination of uric acid under abnormal conditions are rather contradictory, owing to the varying influences of modified diets, and the administration

of medicines and other underlying conditions of treatment. Incorrect methods of analysis have often been the cause of wrong emphasis. It is generally observed that in acute diseases with crises there is an increased elimination of uric acid after the crisis, but a retention during the progress of the disease. In fever there is a steady increase of uric acid in absolute as well as in relative values.[44] Caric arrives at this conclusion from the observation of numerous

44. Caric: Preisschrift, Göttingen, 1888, pp. 1--37.

cases of different diseases. During fasting, Caric observes no difference from the normal in the excretion of uric acid, the uric acid sediment being the result of the high acidity of the urine. Results of other investigators are contradictory.[45] The effect of starvation on the loss of weight of different

45. Hammarsten: Text-book of Physiological Chemistry, translated by Mandel, 1908, p. 570.

organs of the body has also been noted. Voit found that the central nervous system and the heart, organs which are almost in continual activity, suffered practically no loss of weight. Organs rich in nucleo-protein such as the liver, kidney, spleen, and testes lost respectively 53.7%, 26%, 66.7% and 40% to each 100 gms., of fresh organ. Examination of the excreta showed that a greater quantity of protein is destroyed during the first day or two than in subsequent days. This fact is explained on the supposition that the body is at first richly

supplied with "circulating protein" derived from its previous food, and that after this is metabolized the animal lives entirely, so far as protein consumption is concerned, upon its "tissue protein." The "tissue protein" of the kidney, liver and spleen consists essentially of nucleo-protein which when it has undergone decomposition yields the so-called endogenous uric acid. This then might serve as a clue to the origin of endogenous uric acid. It is, however, justifiable only in starvation after the carbohydrate and fat have been exhausted. Whether this same condition of a loss of organs exists in normal metabolism cannot be asserted.

III. METHOD OF URIC ACID DETERMINATION.

150 c.c. of urine were introduced into a beaker, 37.5 c.c. of the Folin-Shaffer reagent added and the mixture filtered without further stirring or leaving it to stand. The Folin-Shaffer reagent consists of 500 grams of ammonium sulphate, 5 grams of uranium acetate and 60 c.c. of 10% acetic acid in 650 c.c. of distilled water. Ofthe filtrate 150 c.c. were transferred as soon as possible, 7.5 c.c. of concentrated ammonia were added and the mixture allowed to stand for twenty-four hours. The precipitated ammonium urate was then transferred quantitatively to a filter paper consisting of hardened paper and washed with 10% ammonium sulphate to remove the final traces of the urate from the beaker. The Precipitate was washed approximately free from chlorides by means of 10% ammonium sulphate solution, the paper removed

from the funnel, opened, and by means of hot water the precipitate was rinsed back into the beaker in which the urate was originally precipitated. The volume of the fluid was at this point about 150 c.c. The solution was allowed to cool at room temperature, 15 c.c. of concentrated sulphuric acid added and titrated at once with N/20 potassium permanganate, $K_2 Mn_2 O_8$, solution. The first tinge of pink color which extended throughout the fluid after the addition of two drops of the permanganate solution, while stirring with a glass rod, was taken as the end reaction. The burette reading was taken and the percentage of uric acid present in the urine under examination computed.

IV. EXPERIMENTAL DATA.

The purpose of the experiment was to observe the excretion of uric acid in normal men living on an ordinary mixed diet. Each subject was allowed to select his own diet and then was required to ingest the diet selected during the course of six periods of four days each. The variation in excretion of each individual as well as the average excretion of all the subjects was noted.

Ten university students served as subjects. Quarters were provided where the men could easily be observed as to certain regulations of sleep and diet. The body weights of the subjects ranged from 54 to 77 kilograms. Their ages varied from 19 to 29 years. There were no athletes among the subjects so that no individual took excessive or violent exercise, but all lived the life of the average normal university student.

As was previously stated the diet was a mixed one for all periods. Table I shows the diet for Period I Nov., 29 - Dec., 2. The diet for the remaining periods was approximately the same in all particulars. The fruits consisted of red and white cherries, pineapples, apples, oranges, plums, peaches and pears. Of the meats, some of which were cured and others fresh, there were corned-beef, roast-beef, veal, mutton, beef-steak, chicken, bacon, pork sausage and boiled and roast ham. Soups consisted of pea, consommé, bouillon and vegetable soup. Corn-meal, rice, cream of wheat, oatmeal and cracked wheat composed the cereals. The puddings were custard, starch-cream and rice. Ice-cream was served every 4 days. The vegetables included potatoes, peas, beans, corn and tomatoes. The other constituents were wheat-bread, coffee, milk, cocoa, butter and water. Meat was served twice a day, morning and evening. Soups were served at the noon-meal only and puddings instead of fruits at night, otherwise the same constituents were served at each meal. In some instances the men selected no coffee, while in other cases a subject would, for example, drink coffee for the morning meal and cocoa for the evening meal. In order to make the diet more palatable,

the constituents of the diet were made to vary for each meal for four successive days. The next four days consisted again of the same diet but reversed in the order of constituents. It will be readily seen that the diet was mixed and normal.

For the sake of uniformity in the mode of normal living, each subject was required to carry out a routine daily schedule. They all rose at 6:30 A.M., were weighed and breakfasted at 7:15 A.M. Lunch was served at 12:15 P.M. At 5:00 P.M. each individual was submitted to a clinical examination. Dinner was served at 6:30 P.M. and all subjects retired between 10:30 and 11:00 P.M. Blood tests including blood pressure were made upon each subject at intervals of two weeks. If at any time a subject was found to be abnormal, the experiment upon him was discontinued until he again became normal. This will be seen to be the case with Subjects I and K, Table II, where one period in each is missing.

The experiment was divided into periods of four days each. Urine was collected in 24-hour periods, preserved with powdered thymol and kept in a refrigerator until the entire 24-hour sample had been collected. The urine bottles were then removed, one-half of each sample carefully measured and placed in cold storage. At the end of the four-day period, 4 one-half volumes were combined into a single sample for each subject thus making 10 composite samples for analysis. These composite samples were then analyzed for uric acid.

From the following tables it will be observed that there exists considerable uniformity in the daily excretion of uric acid. Subjects E, F, G, I and J especially exhibit a very constant output. The average daily excretion of Subject F is 0.475 gm., which is the lowest of any of the subjects. J excreted 0.520 gm., I, 0.619 gm., and G, 0.644 gm. It might be supposed that differences in the quantity and kind of food taken would influence the daily excretion of uric acid to a marked degree, but it will be presently shown that this is not the case altogether. Subject F excreted 0.475 gm., of uric acid per 24 hours, while Subject G excreted 0.644 gm., a much greater quantity than that of Subject

F. Table I shows that the diets of Subjects F and G are very similar in many respects , the main differences being that A ingested somewhat more meat, potatoes and milk. This shows that in this case the variation in the excretion of the uric acid was probably not due entirely to the influence of the diet. The average daily excretion of Subject E is 0.660 gm., the maximum output of uric acid observed during the experiment, yet the diet of this subject varies but little from that of Subjects G and I. Subject J differs more from Subject E in the matter of diet than either Subjects F, or G, yet Subject J excreted a greater average quantity of uric acid than Subject F, but less than Subjects E and G. Subject A also differs in diet from Subject I being somewhat higher in quantity and constituents, but Subject A excreted nearly the same average quantity of uric acid in 24 hours. Here again it might be supposed that differences in diet would produce a variation in the excretion of uric acid, causing the excretion of Subject I to be markedly higher, but this is not the case, inasmuch as the uric acid excretion of Subject I is only 0.004 gram higher than that of Subject A. This difference is hardly commensurate with the variation in the ingested food. It will be noticed then that individuality in these cases plays an important part in the variation of the excretion of uric acid. This variation is probably due to a variation in the endogenous portion of the uric acid excretion, which is governed largely by the individuality of the subject as was mentioned on a foregoing page of this paper.

Subjects A, B, C, H and K show less uniformity in the daily excretion of uric acid than the other subjects. Subject A excreted on the average 0.615 gm., per day. This subject also shows a gradual increase in uric acid output up to the last period at which time there was a slight decrease. Subject B excreted on the average 0.588 gm., with considerable irregular variation. The average excretion of Subject C was 0.597 gm., with a gradual decrease for the first four periods followed by two periods of higher excretion. Subject H exhibited a peculiarity. The excretion averaged 0.608 gm., but the daily excretion varied

alternately. In the first period there was a high excretion, i. e., 0.621 gm., while Period II was lower, i. e., 0.597 gm. Then again Period III returned to an excretion of 0.633 gm., almost the same as for Period I and Period IV showed an excretion of 0.583 gm., similar to that of Period II. Beginning with Period I every alternate period exhibited a striking uniformity in the excretion of uric acid, for example, 0.621, 0.633 and 0.627 gram and 0.597, 0.583 and 0.586 gram for the alternate periods. Subject K showed an average excretion of 0.651 gm., with a general tendency for the daily elimination of uric acid to increase. Subject K excreted the second largest average quantity of uric acid in 24 hours, although the diet does not differ from that of some of the other subjects except in the large quantity of milk ingested and from the fact that no cocoa nor cereals were taken. The diets of Subjects A, B, C and H also are very uniform in quantity as compared with the diets of the other subjects yet there are variations in the excretion of uric acid, some of the quantities being greater than those of Subjects F, G, I and J. Here again, as in Subjects E, F, G, I and J, the same reason for this individual variation in excretion may be given. There is probably no other factor which influences these variations to such an extent as does the individuality of the subject.

Concerning the average daily quantity of uric acid excreted by all subjects, it can be readily seen from the following tables that it does not amount to 0.7 gm., as is generally stated to be the average 24-hour output of uric acid for a normal man. The lowest quantity excreted, (0.475 gm.) was by Subject F, while the greatest quantity (0.660 gm.) was by Subject E.

Subject.	Average Uric Acid Excretion (gms. in 24 hrs.)
F	0.475
J	0.520
B	0.588
C	0.597
H	0.608
A	0.615
I	0.619
G	0.644
K	0.651
E	0.660
Total	5.977
Grand Average	0.597

In no case did the average daily excretion amount to 0.7 gm. The average excretion for all the subjects was found to be 0.597 gm.

V. CONCLUSIONS.

1. The excretion of uric acid in normal men is subject to considerable variation.

2. The variation in the excretion of uric acid by normal men living on a constant and mixed normal diet is due principally to differences in individuality.

3. This variation in excretion occurs probably as a variation in the endogenous uric acid output.

4. The average daily excretion of uric acid for the ten men of the investigation was 0.597 gram, a value somewhat lower than the generally accepted average of 0.7 gram for such a period.

DIET FOR PERIOD I. Nov., 29 - Dec., 2, 1907.

Subjects A to K.

TABLE I.

DIET FOR PERIOD I. Nov., 29 - Dec., 2, 1907.

Subjects A to K.

Subject	A	B	C	E	F	G	H	I	J	K	
Fruits	999.0	995.0	995.0	995.0	995.0	995.0	995.0	995.0	995.0	995.0	
Cereals	1300.0	1300.0	1300.0	1300.0	1300.0	1300.0	650.0	1300.8	975.6		
Meat	820.8	820.8	547.2	820.8	615.6	820.8	820.8	820.8	820.8	568.8	
Potatoes	840.0	840.0	840.0	840.0	630.0	840.0	840.0	840.0	840.0	368.8	
Vegetables	225.0	300.0	300.0	300.0	300.0	300.0	300.0	300.0	300.0	150.0	
Puddings	375.0	375.0	783.0	375.0	375.0	375.0	375.0	375.0	312.6	343.8	
Soups	608.0	608.0	608.0	608.0	608.0	608.0	356.0	608.0	608.0	608.0	
Bread	800.0	560.0	720.0	1330.9	480.0	541.7	800.0	698.5	880.0	876.1	
Milk	2683.2	2683.0	2683.2	2683.2	1238.0	2559.4	4024.8	2683.2	1692.5	4024.8	
Coffee								473.0	472.0		
Cocoa	662.8	662.7	662.7	662.8	662.8	662.8		662.8	662.8		
Butter	199.6	252.9	173.7	357.7	293.4	368.7	217.7	77.9	181.5	281.2	
Water											

TABLE II.

SUBJECT A.

Period	Date	Volume of Urine. c. c.	Specific Gravity	Uric Acid in grams. 96 hours	Uric Acid in grams. 24 hours	Uric Acid Nitrogen in 24 hours.	Remarks.
I	Nov. 29- Dec. 2.	5660	1018	2.260	0.565	0.189	
II	Dec. 3-6	4163	1022	2.216	0.554	0.185	
III	Dec.7-10	4473	1021	2.324	0.581	0.194	
IV	Dec.11-14	4050	10275	2.524	0.631	0.211	
V	Dec.15-18	3705	10275	2.864	0.716	0.239	
VI	Dec.19-22	5579	1018	2.576	0.644	0.215	
Total		27630	61340	14.764	3.691	1.233	
Average		4605	10223	2.461	0.615	0.206	

SUBJECT B.

Period	Date	Volume of Urine. c. c.	Specific Gravity	Uric Acid in grams. 96 hours	Uric Acid in grams. 24 hours	Uric Acid Nitrogen in 24 hours.	Remarks.
I	Nov. 29- Dec. 2.	3797	1023	2.268	0.567	0.189	
II	Dec. 3-6	3604	1024	2.268	0.567	0.189	
III	Dec. 7-10	3389	1027	2.456	0.614	0.205	
IV	Dec.11-14	3926	1026	2.336	0.584	0.195	
V	Dec.19-22	3012	1029	2.400	0.600	0.200	
VI	Dec.23-26	3498	1028	2.371	0.593	0.198	
Total		21226	6157	14.099	3.525	1.176	
Average		3537.6	10261	2.350	0.588	0.196	

TABLE II. (Cont.)

SUBJECT C.

Period	Date.	Volume of Urine. c. c.	Specific Gravity.	Uric Acid in grams. 96 hours.	Uric Acid in grams. 24 hours.	Uric Acid Nitrogen in 24 hours.	Remarks.
I	Nov. 29- Dec., 2.	4939	1019	2.644	0.661	0.221	
II	Dec. 3-6	4468	1018	2.304	0.576	0.192	
III	Dec. 7-10	4574	1018	2.300	0.575	0.192	
IV	Dec. 11-14	4223	10235	2.220	0.555	0.185	
V	Dec. 15-18	4623	1021	2.440	0.610	0.204	
VI	Dec. 19-22	4845	1022	2.416	0.604	0.202	
Total		27672	6133	14.324	3.581	1.196	
Average		4912	1022	2.387	0.597	0.199	

SUBJECT E.

I	Nov. 29- Dec., 2.	8622	1010	2.700	0.675	0.226	
II	Dec. 3-6	6720	1017	2.728	0.682	0.228	
III	Dec. 7-10.	5942	1015	2.644	0.661	0.221	
IV	Dec. 11-14	7130	10155	2.868	0.717	0.240	
V	Dec. 15-18	6752	1016	2.476	0.619	0.207	
VI	Dec. 19-22	6419	10175	2.412	0.603	0.201	
Total		41585	60910	15.828	3.957	1.323	
Average		6930.8	101516	2.638	0.660	0.221	

TABLE II (Cont.)

SUBJECT F.

Period.	Date.	Volume of Urine. c. c.	Specific Gravity.	Uric Acid in grams. 96 hours.	Uric Acid in grams. 24 hours.	Uric Acid Nitrogen in 24 hours.	Remarks.
I	Nov.29-Dec.,2.	4482	1017	1.912	0.478	0.160	
II	Dec.3-6	5043	1012	1.824	0.456	0.152	
III	Dec.11-14	6374	1015	1.884	0.471	0.157	
IV	Dec.15-18	6517	1014	2.068	0.517	0.173	
V	Dec.19-22	7535	10125	1.804	0.451	0.151	
VI	Dec.23-26	6790	1013	1.904	0.476	0.159	
Total		36741	60835	11.396	2.849	0.952	
Average		6124	10139	1.899	0.475	0.159	

SUBJECT G.

I	Nov.29-Dec.,2.	3249	1027	2.824	0.706	0.236	
II	Dec.3-6	3258	1025	2.440	0.610	0.204	
III	Dec.7-10	2944	1029	2.584	0.646	0.216	
IV	Dec.11-14	3160	1031	2.572	0.643	0.215	
V	Dec.15-18	2806	1030	2.640	0.660	0.220	
VI	Dec.19-22	3364	1029	2.388	0.597	0.199	
Total		18781	6171	15.448	3.862	1.290	
Average		3130	1028	2.575	0.644	0.215	

TABLE II (Cont.)

SUBJECT H.

Period.	Date.	Volume of Urine c. c.	Specific Gravity.	Uric Acid in grams 96 hours.	Uric Acid in grams 24 hours.	Uric Acid Nitrogen in 24 h hours.	Remarks.
I	Nov.29-Dec.,2	7504	1011	2.484	0.621	0.207	
II	Dec.3-6	6409	1012	2.388	0.597	0.199	
III	Dec.7-10	6033	1014	2.532	0.633	0.211	
IV	Dec.11-14	6090	10195	2.332	0.583	0.195	
V	Dec.15-18	5455	10205	2.508	0.627	0.209	
VI	Dec.19-22	5732	1020	2.344	0.586	0.196	
Total		37223	60970	14.588	3.647	1.217	
Average		6203.8	10161	2.431	0.608	0.203	

SUBJECT I.

I	Nov.29-Dec.,2.	5701	1013	2.476	0.619	0.207	
II	Dec.3-6	5083	1012	2.452	0.613	0.205	
III	Dec.7-10	6373	1012	2.536	0.634	0.212	
IV	Dec.11-14	5203	1023	2.456	0.614	0.205	
V	Dec.15-18	5206	10175	2.464	0.616	0.206	
Total		27566	50775	12.384	3.096	1.035	
Average		5513.2	10155	2.477	0.619	0.207	

TABLE II. (Cont.)

SUBJECT J.

Period	Date	Volume of Urine. c. c.	Specific Gravity.	Uric Acid in grams.		Uric Acid Nitrogen in 24 hours.	Remarks.
				96 hours.	24 hours.		
I	Nov. 29-Dec., 2.	6819	1013	2.060	0.515	0.172	
II	Dec. 3-6	5360	1016	1.912	0.478	0.160	
III	Dec. 7-10	5059	1018	2.144	0.536	0.179	
IV	Dec. 11-14	5179	1022	2.112	0.528	0.176	
V	Dec. 15-18	4446	1023	2.204	0.551	0.184	
VI	Dec. 19-22	5658	1020	2.048	0.512	0.171	
Total		32521	6112	12.480	3.120	1.042	
Average		5420.1	1002	2.080	0.520	0.174	

SUBJECT K.

Period	Date	Volume of Urine. c. c.	Specific Gravity.	Uric Acid in grams. 96 hours.	Uric Acid in grams. 24 hours.	Uric Acid Nitrogen in 24 hours.	Remarks.
I	Nov. 29-Dec., 2.	4709	1017	2.152	0.538	0.180	
II	Dec. 3-6	3412	1025	2.500	0.625	0.209	
III	Dec. 7-10	4432	1020	2.728	0.682	0.228	
IV	Dec. 11-14	3632	10265	2.536	0.634	0.212	
V	Dec. 19-22	4042	1023	3.104	0.776	0.259	
Total		20227	51115	13.020	3.255	1.088	
Average		4045.4	10223	2.604	0.651	0.218	